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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,741	12/10/2003	Thomas M. Schmitt	2223-171	5362

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,741	SCHMITT ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13,17,22 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 13, 17, 22, 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendments to the claims filed on February 06, 2008 have been entered. Claims 1-11, 14-16, 18-21, 23-49 have been canceled, while claim 13 has been amended.

Claims 12, 13, 17, 22, 50-53 are pending and under current examination.

This action is non-Final.

Election/Restrictions

Applicant's response to the Restriction was received on 12/20/2004. Applicants elected the subject matter of group I, drawn to a method of forming cells of the T cell lineage. Claims 18-21, 23, and 25-28 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1-17, 22 and 24 were examined, while the examiner in the interests of compact prosecution rejoined claim 22.

Claim Objections

Claims 13, 17, 50-53 are objected to because of the following informalities: In the instant case, as recited dependent claims appear to be dependent on multiple claims as dependent claims recite "a method as claimed in .." which should be changed to "The method of claim ... Appropriate correction is required.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 52 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is indefinite in recitation of limitation isolating increased number of the T cell lineage, where the number of cells is increased by at least about 10 to 15 fold. In the instant case, as recited it is unclear as to the number of cells is increased at least about 10 to 15 fold as compared to what reference point. It is unclear if fold increase is as compared to co culture that does not uses OP-9 stromal cell transformed with notch ligand or compared to co culture with OP-9 stromal cell that is not transformed with DL-1 or DL-4. Specific recitation of mature or immature T cell lineage cells showing fold increase in number as compared to method step that defines the reference to which cells are compared on the co-culture would obviate the basis of the rejection. Claims 52 and 53 have been included in the rejection as they depend on independent claims 22. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-13, 17, 50 and 51 remain rejected under 35 U.S.C. 103(a) and claims 22, 55 and 53 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over Jaleco et al (2001, J. Exp. Med. 194:991-1001, IDS), Nakano et al

(1994, Science 265:5175 IDS), Pui et al (Immunity. 1999, 11(3):299-308) and Tatsumi et al (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS).

Applicants' arguments filed on February 6, 2008 have been fully considered but are not persuasive.

As an initial matter, claims 22, 52 and 53 previously indicated as allowable have been also included in the rejection upon further consideration because of following reasons: Claims 22 as recited embrace a method of expanding cells of T cell lineage by using the co culture system of the invention comprising culturing human progenitor cells with OP-9 stromal cells that express DL-1 to produce immature and mature T cell lineage cells and isolating increased number of T cell lineage which is increased by about 10 to 15 fold. As stated before recitation of 10-15 fold increase is indefinite to the extent it is not apparent whether this fold increase is compared to control group of cells or any other reference step. Additionally, one of ordinary who would modify the method of Jaleco to substitute S-17 stromal cell that express DL-1 with another OP-9 would implicitly observe higher number of immature T lineage cells. Thus, subsequent analysis is limited to the extent claims read on a method of culturing human progenitor/stem cells with OP-9 stromal cells that express Delta-1 to produce mature and immature/mature T lineage cells.

It is noted that Applicants agree that Jaleco et al teaches that culturing human progenitor cells with mouse S-17 stromal cells that express Delta-1 (S-17-DL1) produces low levels of CD3+ CD4+ CD8+ T-lineage cells (see page 5, last para.). This supports the Examiner's argument that co culturing progenitor cells with stromal cell that express DL-1 to study T-lineage cells was known in prior art.

Applicants' argue that OP9 cells generated about 65% double positive cells while the S-17 DL1 cells only generated about 5% double positive cells. Therefore, based on the low level of T cell generated by Jaleco one of ordinary skill in the art would not be motivated to use murine stromal cell n order to prepare mature T cells

claimed in claims 12 (see argument page 6, para. 1). Applicants also assert that inventors have unexpectedly demonstrated that OP-9DL-1 cells were able to induce differentiation of stem cells to mature T cells.

In response, with respect to claim 22, it is noted that claims are not limited to mature T cells lineage rather method embraces expanding immature as well as mature cells of T-cell lineage. It would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to substitute S-17 stromal cell taught by Jaleco et al with another OP-9 stromal cells with reasonable expectation to study the expansion of immature and or mature T cell as stated in previous office actions.

It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the states of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors.

Examiner would agree with the applicants' assertion that prior art of Jaleco taught culturing human progenitor cells with mouse S-17 stromal cells that express Delta-1 (S-17-DL1)to produces low levels of immature CD3+ CD4+ CD8+ or double positive T-lineage cells, and thus differed from claimed invention by failing to produce mature T lineage cells as required by claim 12. However, applicant's argument that substitution of one stromal cell (S-17) taught by Jaleco with another OP-9DL-1 resulted in unexpected production of mature T lineage cells is not fully persuasive. With respect to OP-9, contrary to applicants' arguments, it was generally known that OP-9 stromal cells provide a practical model system for the induction of lymphopoiesis from several sources of progenitors. Specifically, Nakano et al provided guidance with respect to OP-9 cells that could support haemato lymphopoiesis from embryonic stem cells, while Pui et al provided evidence that

indicated a crucial role for Notch signaling in the T- versus B-cell fate decision. Specifically, Pui showed that B-cell development is abolished in mice that are reconstituted with bone-marrow progenitors expressing a constitutively active form of Notch, and instead, CD4+CD8+ DP T cells develop in the bone marrow of these mice (see figure 3 and 5 of Pui et al). Given that it was known to one of ordinary skill the important role for Notch signaling at various stages of T-cell development, it is reasonable to state that one of ordinary skill in the art to substitute SL-17 stromal cell with another OP-9 that expresseDL-1 in determining the fate or generation of T cells. It is noted that Jaleco et al provided guidance on a method of using an *in vitro* system comprising stromal cells that also promoted selective differentiation of CB CD34+ cells into the B cell lineage, but when these cells were co cultured these SL-17 cells that were modified with Delta-1 ligand to support T cell lymphopoiesis of human hematopoietic progenitor cells (HPCs) without supporting B cell lymphopoiesis (Abstract, pg. 995, Table 1). Given that Pui et al taught constitutive expression of activated Notch1 results in the emergence of a population of thymic-independent T cells in the bone marrow, concurrent with an early and persistent block in B cell maturation, it would be apparent to one of ordinary skill in the art to substitute one stromal cell (SL-17) that expresses notch ligand (DL-1) with another stromal cell such as OP-9 that express notch ligand to study the role of T cells lymphopoiesis of human hematopoietic progenitor cells with reasonable expectation of achieving predictable results.

Applicants also cite post filing review article (Zungia-Pflucker, 2004, art of record) to indicate the state of art indicating that T cells could not be generated from stem cells using a simple stromal cell monolayer" (see page 70, column 1). The inventors unexpectedly demonstrated that OP9-DL1 cells were able to induce the differentiation of stem cells to mature T cells. This invention is clearly advantageous over the prior art as it provides a simple yet efficient culture system that greatly facilitates the generation of T cells.

In response, it is noted that claim 22 is not limited to mature T cells, rather it embraces cells that are clearly taught in prior art (see Jaleco), thus with respect to claims 22, 52 and 53 applicants' arguments are not commensurate with the scope of the claims.

Examiner would agree with applicant's assertion that T cells could not be generated from stem cells using a simple stromal cell monolayer. However, it is not the stromal cell alone that is capable of generating T cell rather as noted in post filing art and also disclosed by Pui that shows the importance of Notch signaling in the T- versus B-cell fate decision. As stated before, Pui showed that B-cell development is abolished in mice that are reconstituted with bone-marrow progenitors expressing a constitutively active form of Notch, and instead, CD4+CD8+ DP T cells develop in the bone marrow of these mice (Supra). This is also emphasized by applicants' cited art of Zungia-Pflucker et al that states, "Notch 1- deficient mice show a severe block in T-cell development, with the concomitant development of B cells in the thymus" (see page 69, col. 1, para. 3 under notch ligand). Additionally, it is also disclosed that Notch signals have been shown to promote the development of the αβT-cell lineage over that of the γδ-T-cell lineage, to regulate rearrangement of the T-cell receptor-β (TCR-β) gene4, and to influence the CD4+ versus CD8+ T-cell fate decision (see page 69, col. 1, last para. bridging to col . 2, para. 1). Taken together it is reasonable to assert that it is not only stromal cell but stromal cell that expresses notch ligand that has a crucial role in T-cell-lineage commitment and differentiation. Given the fact that one of ordinary skill in the art was aware the use of co culturing of progenitor cells with stromal cell that expresses notch ligand to generate cells of T cell lineage was known. It would have been obvious for one or ordinary skill in the art to substitute one stromal cell (SL-1) that expresses DL-1 with another functionally equivalent stromal cells such as OP-9 with reasonable expectation of producing cells of T cell lineage particularly in view Pui who teach expression of activated Notch1 would result in the emergence of a

population of thymic-independent T cells in the bone marrow, concurrent with an early and persistent block in B cell maturation. With respect comparative data provided in the example 9 of the instant application, it is noted that data shows under similar condition both stromal layer are capable of producing B cells with equal efficiency from HPCs cultured on control OP9-GFP or S17-GFP cells. However, there was a marked difference in the generation of T cells on S17-DL1 cells (5% DP cells) as compared to OP9-DL1 cells (65% DP cells). In the instant case, the claimed method is directed to a method of forming cells of T cell lineage, irrespective of efficiency of the system. The evidence provided in the specification teaches better efficiency of producing cell of T cell lineage on OP-9; however, it does not preclude generation of T cells on S17-DL1. Applicants have not provided evidence to demonstrate that condition that produces T cells of different lineage (cell type, incubation time, growth medium and other condition) on OP9-DL1 would not be produced under similar cells on S17-DL1. It is emphasized that method of forming T cell on functionally equivalent stromal cell may be of varying efficiency, however, its production under similar condition is not unexpected. MPEP 2145 states "If a prima facie case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case. See, e.g., In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Rebuttal evidence and arguments can be presented in the specification, ... or by way of an affidavit or declaration under 37 CFR 1.132, e.g., Soni, 54 F.3d at 750, 34 USPQ2d at 1687; In re Piasecki, 745 F.2d 1468, 1474, 223 USPQ 785, 789-90 (Fed. Cir. 1984). In absence of any objective evidence or declaration the rejection of record is maintained.

With respect to applicants' assertion that previous examiner indicated claim 12 being allowable if amended to recite mature T cells, it is emphasized that prosecution was reopened in view of further consideration on the objective evidence presented of unexpected result presented by the applicants. Additionally, claims 22

is included in the rejection as it fails to recite comparative step rendering claim indefinite and also claimed method embrace both immature and mature T cells.

Conclusion

Examiner's comment: It is noted that preamble of claim 12 recites a method of forming T cell lineage; while method steps result in formation of only mature T cells lineages. Thus, preamble of the claim 12 is not commensurate with the scope of the resulting cells. Recitation of preamble commensurate with the scope of resulting mature T cell is advised.

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Pykett et al US Patent No. 7067316, dated 6/27/2006, effective filing date 9/25/1998).

Cho et al Lymphohematopoietic differentiation from embryonic stem cell in vitro (Dissertation, 2001, 62, 128 pages)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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